15. The DNA of Claim 14, further consisting essentially of a base sequence encoding the amino acid sequence H-Gly-Ser-Gly covalently bound to the H-Cys amino acid through a peptide bond.

16. The DNA of Claim 14, further consisting essentially of a base sequence encoding the amino acid sequence H-Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly covalently bound to the H-Cys amino acid through a peptide bond.

17. The DNA of Claim 16, further consisting essentially of a base sequence encoding the N-terminal amino acid sequence:

His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg Lys.

18. The DNA of Claim 16, further consisting essentially of a base sequence encoding the N-terminal amino acid sequence:

Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu Leu Leu Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser.

19. The DNA of Claim 14, having the following base sequence:

TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

20. The DNA of Claim 15, having the following base sequence:

GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

21. The DNA of Claim 16, having the following base sequence:

AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

22. The DNA of Claim 17, having the following base sequence:

CAC CCG CTG GGC AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC GGG TTA CAG GAG CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG CTG CAG GTG GAG CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC CCC CGT CCC ACA GGT GTC TGG AAG TCC CGG GAG GTA GCC ACC GAG GGC ATC CGT GGG CAC CGC AAA ATG CTC CTC TAC ACC CTG CGG GCA CCA CGA AGC CCC AAG ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.

23. The DNA of Claim 18, having the following base sequence:

ATG GAT CCC CAG ACA GCA CCT TCC CGG GCG CTC CTG CTC CTG CTC
TTC TTG CAT CTG GCT TTC CTG GGA GGT CGT TCC CAC CCG CTG GGC
AGC CCC GGT TCA GCC TCG GAC TTG GAA ACG TCC GGG TTA CAG GAG
CAG CGC AAC CAT TTG CAG GGC AAA CTG TCG GAG CTG CAG GTG GAG
CAG ACA TCC CTG GAG CCC CTC CAG GAG AGC CCC CGT CCC ACA GGT
GTC TGG AAG TCC CGG GAG GTA GCC ACC GAG GGC ATC CGT GGG CAC
CGC AAA ATG GTC CTC TAC ACC CTG CGG GCA CCA CGA AGC CCC AAG
ATG GTG CAA GGG TCT GGC TGC TTT GGG AGG AAG ATG GAC CGG ATC
AGC TCC TCC AGT GGC CTG GGC TGC AAA GTG CTG AGG CGG CAT.--

SUPPORT FOR AMENDMENTS

Support for Claims 14-16 and 19-21 can be found in the present specification on page 3, lines 2-13, page 6, lines 13-15, and in Figure 2 as originally filed. Support for Claims 17-18 and 22-23 can be found in the present specification on page 6, lines 13-19, in Figure 2 as originally filed and in Claims 3 and 4 as originally filed. Additional support for Claims 21-23 can be found in Claims 5-7 as originally filed. Thus, no new matter is introduced by the present Amendment.

Claims 14-23 have been added. Thus, Claims 2-7 and 10-23 are active in the present application.

REMARKS

The present invention concerns a DNA consisting essentially of, or alternatively, a recombinant DNA sequence comprising a base sequence encoding a polypeptide having one of the following amino acid sequences:

(1) H-Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH;

(2) H Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His-OH;

(3) Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His;

(4) His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser Gly Leu Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg Lys Met Val Leu Tyr Thr Leu Arg Ala Pro Arg Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu; and

(5) Met Asp Pro Gln Thr Ala Pro Ser Arg Ala Leu Leu Leu Leu Leu Phe Leu His Leu Ala Phe Leu Gly Gly Arg Ser His Pro Leu Gly Ser Pro Gly Ser Ala Ser Asp Leu Glu Thr Ser Gly Led Gln Glu Gln Arg Asn His Leu Gln Gly Lys Leu Ser Glu Leu Gln Val Glu Gln Thr Ser Leu Glu Pro Leu Gln Glu Ser Pro Arg Pro Thr Gly Val Trp Lys Ser Arg Glu Val Ala Thr Glu Gly Ile Arg Gly His Arg Lys Met Val Leu Tyr Thr Leu Arg Ala Pro Arg Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His.

Applicants thank Examiner LeGuyader for the helpful and courteous discussion held with their U.S. representative on June 30, 1993. In accordance with remarks made, Applicants submit herewith Seilhamer et al, U.S. Patent No. 5,114,923, corresponding to continuation-in-part application Serial No. 460,855, filed May 31, 1989. Applicants' representatives have tried to obtain copies of the parent applications to Seilhamer et al to investigate the disclosures therein. However, the file wrappers of U.S. application Serial Nos. 299,880, filed January 19, 1988, 206,470, filed June 14, 1988, and 200,383, filed May 31, 1988, are unavailable.

Applicants cannot determine whether any relevant disclosure in Seilhamer et al is also present in the parent applications, and as a result, possibly known prior to the effective filing date of the presently claimed invention. Accordingly, Seilhamer et al cannot be applied at this time as a reference against the present invention. The burden is on the Examiner to prove that information relevant to the present claims was known to others prior to the effective filing date of the present application.

Furthermore, as discussed, Seilhamer et al appear to teach away from the process taken by the present Inventors in obtaining the presently claimed DNA sequences. For example, Seilhamer et al repeatedly teach that porcine brain natriuretic peptide (pBNP) DNA would not hybridize to a human DNA library (see column 8, lines 40-51, column 9, lines 32-35 and 45-47, column 22, lines 67-68). Although the human NRP

gene disclosed in Figures 5-1 and 5-2 of Seilhamer et al contains introns (additional non-coding sequences present in the coding region), Seilhamer et al equate a human genomic library with a human cDNA library (column 8, line 55 through column 9, line 10), thereby indicating that no unusual problems are expected in screening a genomic library. Furthermore, Seilhamer et al suggest that no human DNA will successfully hybridize with DNA encoding pBNP (column 22, lines 67-68). Accordingly, viewing the teachings of Seilhamer et al as a whole, one of ordinary skill in the art would expect that using DNA encoding pBNP will not lead to a successful screening of a positive clone obtained from a human DNA library of any kind.

On the other hand, the present Inventors successfully screened a human cDNA library with a fragment of porcine cDNA encoding pBNP (page 4, line 21, through page 6, line 2, and page 12, line 2 from the bottom, through page 16, line 16 of the present specification). Thus, in view of the failure of Seilhamer et al to hybridize DNA encoding pBNP to human DNA, the success of the present Inventors to obtain DNA encoding human BNP is surprising and unexpected. The following remarks shall further summarize and expand upon topics discussed.

The rejection of Claims 2-7 and 10-13 under 35 U.S.C. 103 as being unpatentable over Maekawa et al in view of Maniatis, Sudoh et al, (R) and Sudoh et al (T), Oikawa et al and Vlasuk et al is respectfully traversed.

Maekawa et al disclose cloning and sequence analysis of cDNA encoding a precursor for porcine brain natriuretic peptide (pBNP). Sudoh et al (R) disclose the sequences of porcine BNP and human α-ANP (atrial natriaretic peptide). Sudoh et al (T) disclose a 32-amino acid-long brain natriuretic peptide identified in porcine brain. Oikawa et al disclose the structure of dog and rabbit precursors of atrial natriuretic peptides deduced from nucleotide sequences of cloned cDNA. Vlasuk et al disclose the structure and analysis of the bovine atrial natriuretic peptide precursor gene.

Maniatis et al teach the expression of eucaryotic genes, vectors that express fused and unfused eucaryotic proteins, and synthetic oligodeoxynucleotides useful for hybridizing to (and screening) mRNA. The method of screening mRNA disclosed by Maniatis et al is essentially the method disclosed by Suggs et al, cited against the present invention by the Examiner in parent application Serial No. 07/486,827, and withdrawn by the Examiner in the present application. Similar to the teachings of Suggs et al, one must scan the known protein sequence for areas rich in amino acids specified by one or two codons (page 226, lines 3-6 from the bottom). The oligonucleotides of Maniatis et al, similar to those of Suggs et al, form hybrids only with those species of mRNA to which they are exactly complementary (page 227, lines 4-7).

Therefore, although Maniatis et al suggest that their oligodeoxynucleotides can be used as probes to screen cDNA libraries, the teachings of Maniatis et al fail to cure the

deficiencies of the remaining of the cited references. Prior to the present invention, the amino acid sequence of human BNP was not known. However, the method of Maniatis et al requires that the amino acid sequence be known. Further, without the absolute assurance that there will be at least one probe which is exactly complementary to the target sequence provided by knowledge of the amino acid sequence, success cannot be achieved. One cannot have a reasonable expectation of success using the method of Maniatis et al when the amino acid sequence encoded by the target sequence is not known.

However, assuming *arguendo* that it would have been obvious for one of ordinary skill in the art to use the DNA sequence disclosed by Maekawa et al, or an effective portion thereof (as taught by Seilhamer et al [col. 8, lines 40-54]), as a probe to screen for the human BNP gene, the clear failure of Seilhamer et al to successfully achieve this result attests to the nonobviousness of the present DNA. Interestingly, as discussed above, Seilhamer et al equate a genomic library with a cDNA library, thereby indicating that no unusual problems are expected in screening a genomic library. Even more interesting, the temperature conditions used by Seilhamer et al were less stringent (37-42°C; col. 9, lines 6-10 and 38-42) than those used to obtain the present DNA sequences (60°C; page 14, line 19 of the present specification).

The teachings of Seilhamer et al are clearly more relevant to the presently claimed invention than the combined teachings of the cited references, which neither disclose nor

suggest screening a human DNA library with cDNA encoding porcine BNP. Therefore, the combined teachings of the cited references do not overcome the evidence of the difficulties encountered in obtaining the present invention as described by Seilhamer et al. Therefore, this ground of rejection is unsustainable, and should be withdrawn.

Accordingly, the present application is in condition for allowance. Early notice to that effect is earnestly solicited.

Respectfully submitted,

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